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HETEROCYCLES IN BIOACTIVE NATURAL PRODUCTS

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ABSTRACT

The science of natural products has gained enormous ground in their fields and has built up a collection of changes to accomplish their separate objective compounds. Lignans have pulled in a lot of enthusiasm throughout the years because of their wide event in plants and the wide scope of natural exercises. They have critical pharmacological properties, including antitumor, cancer prevention agent, antiviral and cardiovascular activities. Segregation of plant materials remains exceptionally work concentrated cycle and the yields are commonly low. Accordingly, nonstop endeavors for the improvement of engineered techniques are made.

1. CHEMOSELECTIVE CARBON-CARBON COUPLING OF ORGANOCUPRATES WITH (BROMOMETHYL) METHYLMALEIC ANHYDRIDE

Chaetomellic anhydride An and B have been as of late isolated1 from Chaetomella acutiseta, and their dianionic structures are strong and profoundly explicit inhibitors ofras famesylprotein transferase. The arrangement of easy engineered ways to deal with this bioactive natural product, chaetomellic corrosive An anhydride (tetradecylmethylmaleic anhydride) is an assignment of current intrigue. After seclusion of this bioactive compound in 1993 to date nine substitute unions of le, five from abroad and four from our grdtip have been cultivated utilizing assortment of rich techniques (talked about in prior section). As of late, various 2-alkyl-3-methyl subbed maleic anhydrides have been detached as natural products, for example, 2-ethyl-3-methylmaleic anhydride, 2-hexyl-3-methylmaleic anhydride, 2-octyl-3-methylmaleic anhydride, chaetomellic corrosive Clla and some of them show explicit organic exercises. While trying to have a simple admittance to this sort of subbed maleic anhydrides, we arranged an effortless two-advance way to deal with n-alkylmethylmaleic anhydrides through chemoselective carbon-carbon coupling of Grignard reagents with (bromomethyl)methylmaleic anhydride.

Chemoselective Grignard responses, with protection of specific functionalities have been accounted for in the writing. Normant et aln announced cross coupling of Grignard reagent with 2-acetyl bromoethane (3) by saving acetic acid derivation bunch where as Numomoto et a/13 have effectively completed the cross coupling response of 1,3-butadiene-2-ylmagnesium chloride (6) and subbed halide keeping the cyano and ester bunches flawless as demonstrated as follows (Scheme la). Baer et a/14 have detailed the copper catalyzed response of Grignard reagents with chloromagnesium salt of co-bromoacids 8 to get ready assortment of alkylcarboxylic acids with conservation of carboxylic corrosive usefulness.

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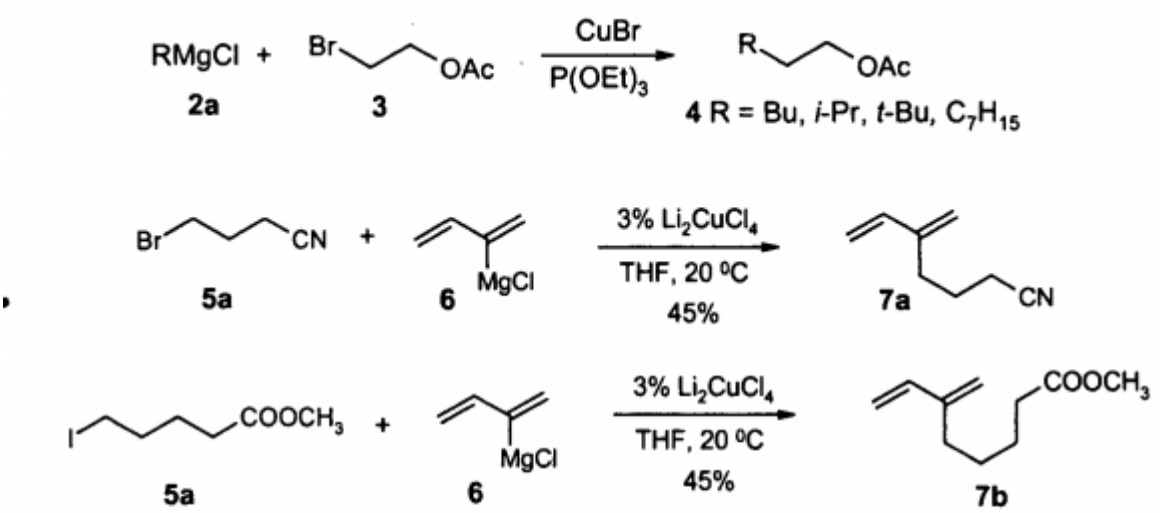
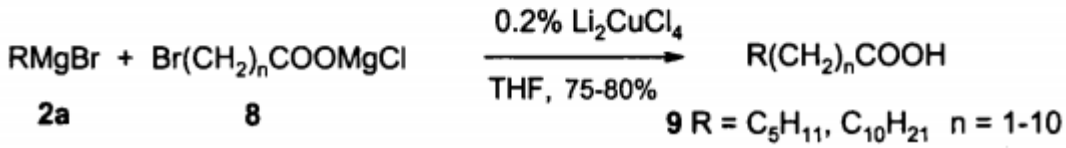
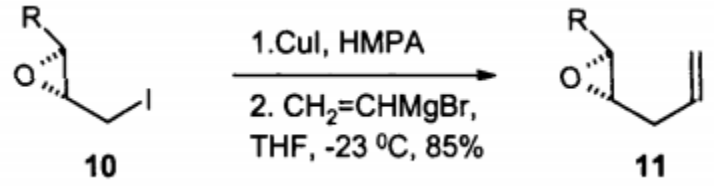


Scheme 1b



Grignard replacement reaction with unblemished conservation of epoxide usefulness has been accounted for just because by Nicolaou et a/15 wherein the moderate expansion of allylmagnesium bromide to a blend of substrate 10, within the sight of synergist measure of Cul (0.1 equiv) and HMPA (4 equiv) in THF at - 23 °C gave solely the replacement product, homoallylic epoxide 11 in 85% yield.



Mori and coworkers have effectively finished the synthesis of pheromones with safeguarding the epoxide by utilizing dialkyllithiumcuprate.

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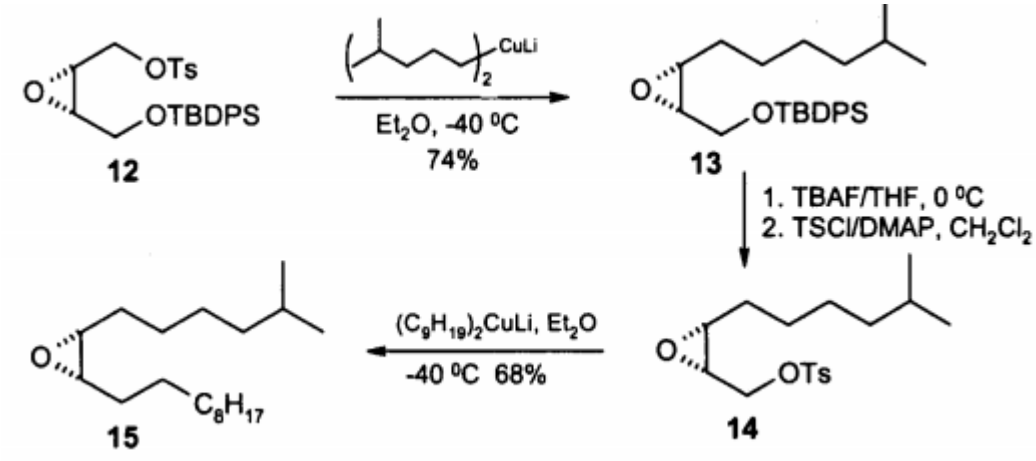
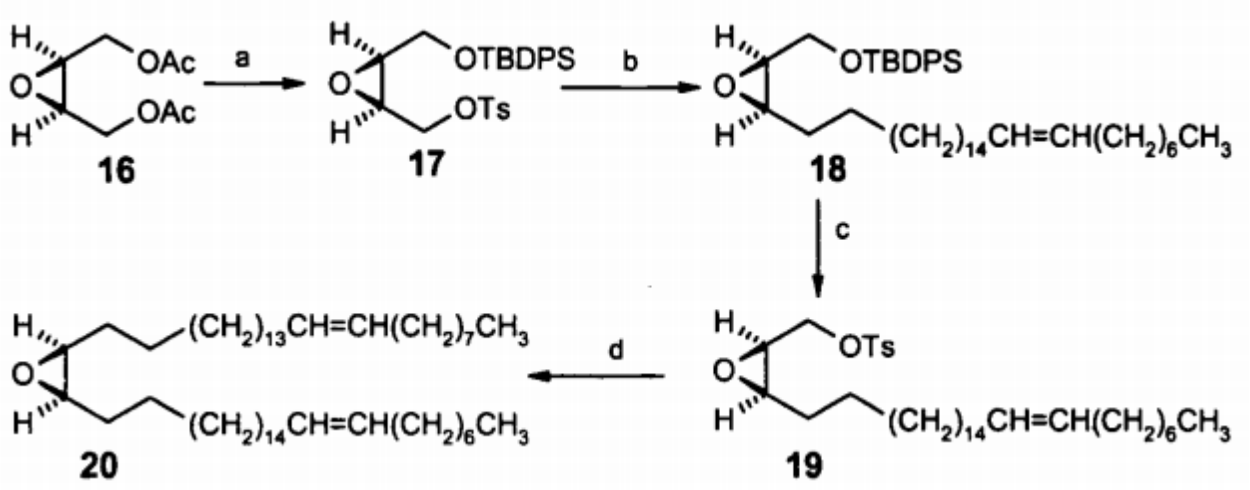


Another report from Mori's gathering has centered around the synthesis of fairy acknowledgment pheromone uses Grignard coupling reaction as a key advance with a flawless conservation of epoxide moiety. The enantiomerically unadulterated epoxy building square 17 has been utilized as a beginning material that thusly was incorporated from meso-diacetate 16 by hilter kilter hydrolysis catalyzed by pig pancreatic lipases (PPL) and a few different advances. Joining of carbon anchor on 17 to get target atom 20 was executed by copper catalyzed Grignard reaction in diethylether within the sight of HMPA. They additionally combined the antipode by adjusting the arrangement of two Grignard coupling reactions.



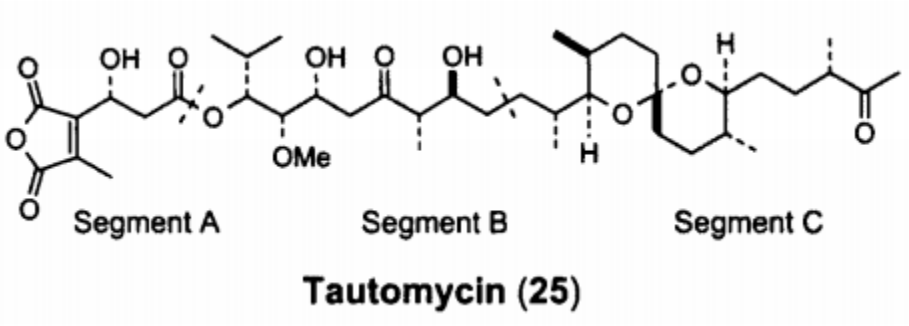
Reagents and conditions: (a) PPL and several other steps; (b) (Z)-Me(CH2)6CH=CH(CH2)i5MgBr, Et20, HMPA, Cul; (c) (i) (Bu)4NF, THF, (ii) TsCl, TEA, DMAP, CH2C12; (d) (Z)-Me(CH2)7CH=CH(CH2),3MgBr, Et20, HMPA, Cul.

2. (±)-2,3-DISUBSTITUTED MALEIC ANHYDRIDE SEGMENT OF ANTIFUNGAL ANTIBIOTIC TAUTOMYCIN

Tautomycin (25) was confined in 1987 by Isono and colleagues from Streptomyces spiroverticillatus as new anti-infection with solid antifungal movement against Sclerotinia sclerotiorm and inhibitory action to protein phosphatase of type 1 and 2A. In 1993 a

similar gathering decided the total configuration of 25 with 13-chiral focuses by utilizing chemical transformations and spectroscopic data. The tautomycin has pulled in an attention of numerous engineered organic scientists in view of its fascinating auxiliary designer and novel natural action. Retrosynthetic examination of tautomycin separated the objective atom into three subunits as appeared in plot 4. Disconnection of an ester bond managed fragment A (left wing), section B (center wing) and portion C (conservative).

The all out synthesis of 25 includes synthesis of three portions A, B and C followed by stepwise coupling of these potential structure squares. To date four all out amalgamations and one late proper absolute synthesis of this atom have been accounted for separated from the related synthesis of tautomycin subunits, for example, 2,3-disubstituted maleic anhydride fragment An and polyketide portion of tautomycin, section B and C.30 According to Chamberlin et al26 the best test in the synthesis of tautomycin is in the construction of simple looking 2,3-disubstituted maleic anhydride portion A. Portion An is profoundly functionalized particle with three carboxylic gatherings and one hydroxy gathering. This β-hydroxy ester is profoundly inclined to dehydration using acidic cr-hydrogen atom to give of unsaturated ester and thus the synthesis of this portion requires an uncommon consideration in picking reagents/reaction Conditions. To date four-multistep synthesis of portion A (26) have been practiced beginning from appropriately 3,4-disubstituted furans, 1,3-propanediol, and even acetylenedicarboxylic ester, utilizing different engineered techniques which have been now talked about in the primary section.



Tautomycin (25)

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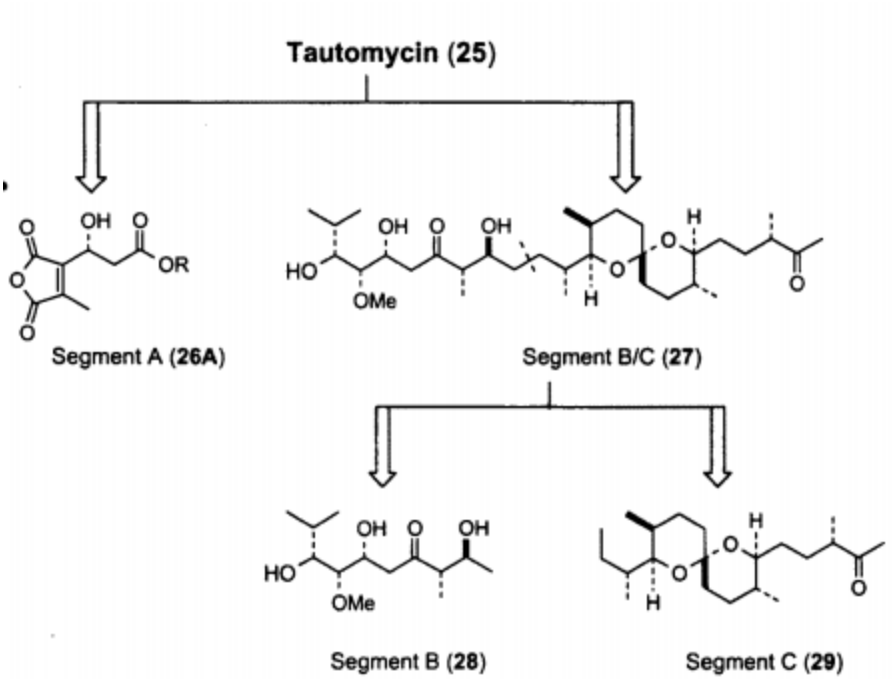
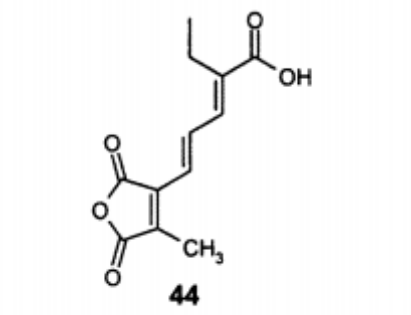


As of late we have effectively completed9 the synthesis of naturally happening alkylmethylmaleic anhydrides including famesyl-protein transferase inhibitor chaetomellic anhydride A beginning from (bromomethyl)methylmaleic anhydride which thus was integrated from dimethylmaleic anhydride as talked about in the previous section of this part. We have additionally detailed the synthesis of fulgenic acid35 beginning from (bromomethyl)methylmaleie anhydride by means of (hydroxymethyl)methylmaleic anhydride (conspire examined in section D of this part). With our notional enthusiasm towards the synthesis of exceptionally oxygenated 2,3-disubstituted maleic anhydride portion An of tautomycin, we arranged two diverse manufactured procedures beginning with (bromomethyl)methylmaleic anhydride and are talked about in detail in the current section. An engaging component of our methodology is a short course synthesis utilizing anhydride to anhydride conversion without including any protection-deprotection science (a current need of time).

3. SYNTHESIS OF 2,3-DIDEHYDROTELFAIRIC ANHYDRIDE

Another methylmaleic anhydride metabolite was detached in 1996 by Edwards bunch from the way of life mechanism of the growth Xylaria telfairii Berk and named as 2,3-didehydrotelfairic anhydride ([r£,3'£)- 2-(4-carboxyhexa-l,3-dienyl)- 3-methylmaleic anhydride, 44). The structure oftelfairic anhydride was resolved based on logical and unearthly data. The organic job for natural product 44 has not been built up however the action displayed by a few other alkylmethylmaleic anhydrides in this arrangement uncover that the synthesis and natural screening of this natural product will be valuable. To date there is no report on the synthesis of this as of late segregated natural product. In pusuit of our progressing program towards the synthesis of natural products having 2-alkyl-3-methylmaleic anhydride as basic skeleton or as a section structure,41 the intriguing structure of 2,3-didehydrotelfairic anhydride grabbed our eye. We intended to invest in engineered amounts of energy to

accomplish the main all out synthesis of this natural product for basic confirmation and organic evaluation.



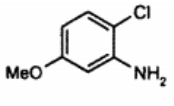
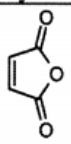
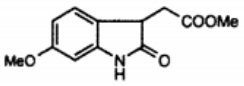
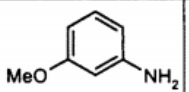
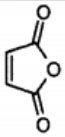
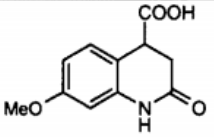
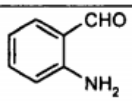
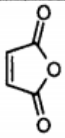
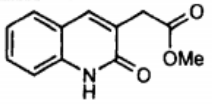
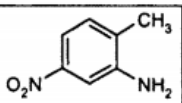
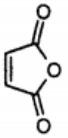
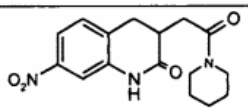
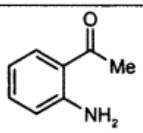
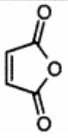
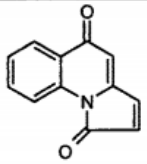
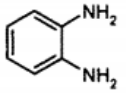
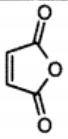
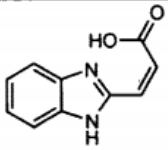
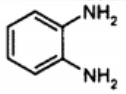
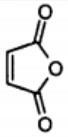
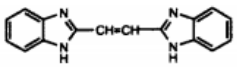
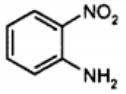
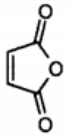
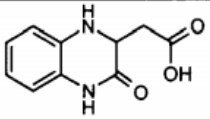
44

2,3-Didehydrotelfairic anhydride

4. α-QUINOXALINYLACRYLIC AND BENZOTHIAZINYLACRYLIC ACIDS

Ring conclusion reactions of appropriately ortho-subbed maleanilic corrosive have been richly utilized for the synthesis of basically intriguing and organically significant heterocycles through intramolecular Michael addition, condensation and dehydrative cyclisation reactions with crucial job of ortho substituents. The multifunctional maleanilic acids are gotten from the reactions of reasonably ortho-subbed aniline subsidiaries (orthosubstituents = H, Cl, CH_3, CHO, COMe, COOH, NH_2, $N0_2$, OH, SH) and assortment of balanced and unsymmetrical maleic anhydrides. The intramolecular cyclisation reactions of these anilic acids have been deliberately concentrated with the generation of carbon-carbon, oxygen-carbon, nitrogen-carbon and sulfur-carbon security. The agent instances of previously mentioned class of reactions are summed up in the accompanying table.

Table 1: Heterocycles Derived from Suitably Substituted Aniline Derivatives and Maleic Anhydrides

Sr. No.	Aniline Derivative	Maleic anhydride	Reaction Condition (% Yield)	Product
1			1. Et_2O, rt 2. $MeOH/H^+$ 3. $Ni(PPh_3)_4$, DMF 50-60 °C, 5 h (61%)	
2			1. Et_2O, rt 2. $h\nu$, MeOH, 5 h (38%)	
3			1. Et_2O, rt 2. $MeOH/H^+$ 3. PPh_3, EtOH, reflux, 4 h. (60%)	
4			1. Et_2O, rt 2. $MeOH/H^+$ 3. piperdineacetate 50-60 °C, 0.5 h (60%)	
5			Xylene, excess TEA, 120-140 °C (90%)	
6			Aq. HCl, reflux (51%)	
7			1. Et_2O, rt 2. *o*-PDA, PPA 220-230 °C (70%)	
8			1. $AlCl_3$,80 –100 °C 2. P_2O_5, MeOH, reflux. 3. Ni/ H_2 , EtOH (82%)	

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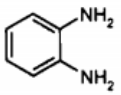
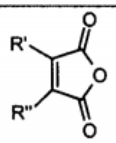
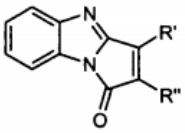
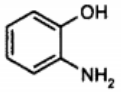
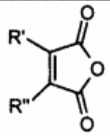
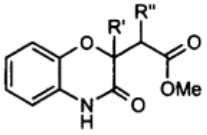
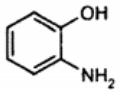
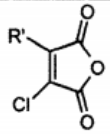
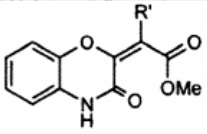
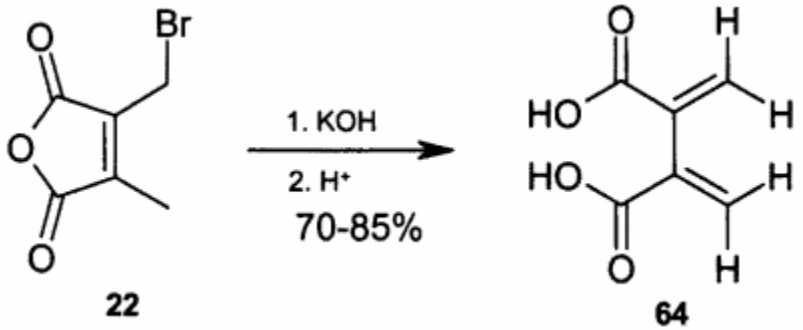
9		 R' = CH_3, Ph, Me, R' = Ph, Me	1.EtOH, reflux 2. AcOH, reflux (95%)	
10		 R'/R" = H, Me	TEA, MeOH, reflux (82%)	
11		 R' = H, Cl	1. Acetone, rt 2. TEA, MeOH, reflux (89%)	

The different models mentioned in the above table uncover that the nucleophilic reactions of balanced and unsymmetrical cyclic anhydrides have given a few fascinating and significant heterocyclic frameworks. It has been settled that the dimethylmaleic anhydride on reaction with essential amine yields the comparing imide where as on reaction with o-phenylenediamine (o-PDA), first the relating imide and afterward pyrrolobenzimidazole, while on reaction with o-aminothiophenol (o-ATP) yields benzothiazinylpropionic corrosive by means of ring opening and intramolecular Michael addition reaction. As of late we have combined (bromomethyl)methylmaleic anhydride (22), which has five substitute destinations for nucleophilic reactions as talked about in section An of this part. We got ready for efficient investigation of chemo-and regioselective nucleophilic reactions of this unsymmetrical anhydride all the more explicitly with reasonably ort/w-subbed aniline subordinates to plan new heterocycles. Aside from the current work to date just a single reaction of (bromomethyl)methylmaleic anhydride (22) is known in writing wherein the bromoanhydride has been richly utilized for the most brief synthesis offulgenic corrosive by means of base actuated 1,4-dehydrobromination.



22 64

5. CONCLUSIONS

We arranged (bromomethyl)methylmaleic anhydride and 2,3-dibromomethylmaleic anhydride through NBS bromination of dimethylmaleic anhydride and in the current dissertation we have shown the engineered utilities of these likely beginning materials without precedent for the field of manufactured organic science. The

chemoselective carbon-carbon coupling of organocuprates with (bromomethyl)methylmaleic anhydride outfitted rasfamesyl-protein transferase inhibitor chaetomellic anhydride An and its analogs in 55-60% yields. Beginning from (bromomethyl)methylmaleic anhydride we incorporated (±)- maleic anhydride section of antifungal anti-infection agents tautomycin in five-steps (28% by and large yield) without utilizing any protection-deprotection science. Beginning from (bromomethyl)methylmaleic anhydride we have finished five-advance synthesis of dihydrotelfairic anhydride by means of chemoselective Wittig reaction with 29% over all yield and our endeavors to dehydrogenate the equivalent to naturally happening telfairic anhydride are in dynamic advancement. In the last section we have considered chemo-and regioselective nucleophilic reactions of (bromomethyl)methylmaleic anhydride with reasonably subbed aniline subsidiaries to structure new heterocycles aquinoxalinylacrylic and tf-benzothiazinylacrylic acids with eliminative generation of new carbon-carbon double security and the current technique will be plentifully valuable to orchestrate a few natural products with this sort of double security.

2,3-Dibromomethylmaleic anhydride (23) has been effectively used to acquire 2,5-dihydro-3,4-furandicarboxylic corrosive. Our investigations to get evenly dialkylsubstituted maleic anhydrides beginning from 23 are likewise in progress.

In the current investigations towards the synthesis of bioactive natural product we effectively utilized the multifunctional (bromomethyl)methylmaleic anhydride as a possible beginning material without utilizing any protection-deprotection science. The current examinations on maleic anhydride science have given us a perfect and clear impression that these multifunctional maleic anhydride moieties have been utilized in the previous century by basically all sort of scientists as likely beginning materials. They go through assortment of reactions and the chemo-, regio-, and enantioselectivities saw with these multifunctional particles are astounding. The advancement of new strong help synthesis/combinatorial science strategies will currently give parcel of new valuable applications of these particles in not so distant future. To put it plainly, maleic anhydride and their subordinates have exceptionally rich history and extremely brilliant present surprisingly in the field of science and profoundly helpful future is guaranteed.

REFERENCES

[1]. Newman DJ, Cragg GM, Snader KM. Natural products as sources of new drugs over the period 1981–2002. J. Nat. Prod. 2003;66:1022–1037.
[2]. Lorence A, Nessler CL. Molecules of interest - Camptothecin, over four decades of surprising findings. Phytochemistry. 2004;65:27 35–2749.
[3]. Pizzolato JF, Saltz LB. The camptothecins. Lancet. 2003;361:2235 –2242.
[4]. Driver RW, Yang LX. Synthesis and pharmacology of new camptothecin drugs. Mini-Rev. Med. Chem. 2005;5:425–439.
[5]. Thomas CJ, Rahier NJ, Hecht SM. Camptothecin: current perspectives. Bioorg. Med. Chem. 2004;12:1585–1604.
[6]. Dallavalle S, Ferrari A, Biasotti B, Merlini L, Penco S, Gallo G, Marzi M, Tinti MO, Martinelli R, Pisano C, Carminati P, Carenini N, Beretta G,

Perego P, De Cesare M, Pratesi G, Zunino F. Novel 7-oxyiminomethyl derivatives of camptothecin with potent in vitro and in vivo antitumor activity. J. Med. Chem. 2001;44:3264–3274.

[7]. Lansiaux A, Leonce S, Kraus-Berthier L, Bal-Mahieu C, Mazinghien R, Didier S, David-Cordonnier MH, Hautefaye P, Lavielle G, Bailly C, Hickman JA, Pierre A. Novel stable camptothecin derivatives replacing the E-ring lactone by a ketone function are potent inhibitors of topoisomerase I and promising antitumor drugs. Mol. Pharmacol. 2007;72:311–319.

[8]. Cagir A, Jones SH, Gao R, Eisenhauer BM, Hecht SM, Luotonin A. A naturally occurring human DNA topoisomerase I poison. J. Am. Chem. Soc. 2003;125:13628–13629.

[9]. Rao VA, Agama K, Holbeck S, Pommier Y. Batracylin (NSC 320846), a dual inhibitor of DNA Topoisomerases I and II induces histone gamma-H2AX as a biomarker of DNA damage. Cancer Res. 2007;67:9971–9979.

[10]. Manpadi M, Uglinskii PY, Rastogi SK, Cotter KM, Wong Y-SC, Anderson LA, Ortega AJ, Van slambrouck S, Steelant WFA, Rogelj S, Tongwa P, Antipin MY, Magedov IV, Kornienko A. Three-component synthesis and anticancer evaluation of polycyclic indenopyridines lead to the discovery of a novel indenoheterocycle with potent apoptosis inducing properties. Org. Biomol. Chem. 2007;5:3865–3872.